Central to the Examiner's comments in the OA are that claims more limited in scope, either by reciting selection of a fraction from multiple fractions or by reciting fractions comprising at least two ingredients are patentable. *See* OA page7, third paragraph and OA at page 10, two thirds down the page. The newly added claims include claims that recite such limitations. Indication of allowance of at least these claims at this time is respectfully requested.

Rejection of Claims under 35 U.S.C. § 103(a).

Claims 32, 40-41, 48-49, 56-59 and 62 are rejected under 35 U.S.C. §103(a) as obvious over Frame *et al*, PRHSJ (1998) ("Frame publication,"), in light of Greenspan, in light of McMurry; claim 47is rejected under 35 U.S.C. 103(a) as being unpatentable over Frame *et al.* (1998) in view of Greenspan *et al.* (1996) in view of McMurray (1992) in view of Habtemarium *et al.* (US 6,225,342) or Kanojia (US 4,046,882 A) and the art, in general.

In particular, the Examiner explains that the Frame publication teaches MA leaves displayed inhibitory activity against M. tuberculosis, but the Examiner recognizes that the publication "did not teach separation of the endogenous components of the M. Americana extract (including elution) to obtain one fraction or more than one fraction, wherein the composition comprises stigmastan-3,5,-diene, friedelin and additionally cyclododecane or acetic acid" (page 4).

The Examiner notes that albeit the cited prior art does not precisely teach the same methods as used by applicant, they teach similar methods and all the methods recited in the claims are generally known, including chromotagraphic separations, elution, usage of one solvent over another on the chromatographic system, identifying specific compounds in the fraction and analyzing for antibacterial activity. Finally, the Examiner explains that there was motivation to identify and isolate the active ingredients, as stated by Frame *et al.* Essentially, the Examiner asserts that the claims are so broad as to cover the whole of the initial plant extract thought by Frame *et al.*

The Applicant respectfully traverses.

As a preliminary comment, the OA seems to go back and forth stating that Frame *et al.* teach an ethanol extract, then a methanol extract. To facilitate the present communication between the Examiner and the Applicant (i.e. Dr. Frame, the same as the author of the prior art), it should be noted that Frame *et al.* publication teaches an ethanol extract and does not mention the possibility or usefulness of an alternative solvent.

There is a second item that needs clarification, as it appears to be critical to the Examiner's arguments. It would appear that a critical concern to the Examiner is the origin of the compounds in Table 5 of the specification. The Examiner erroneously concludes the specification is ambiguous in respect to the origins of the compounds listed in Table 5 of the specification and that the compounds listed in Table 5 are derived from the ethanol extract.

To the contrary, the specification is clear on this point and the compounds listed on Table 5 are derived from the methylene chloride fraction, further separated into active fractions:

> **Methylene chlorine** extracts from ***Mammea Americana,*** *Marchantaceae polymorpha,* or *Callistemon citrinus* **were separated on a HPLC system**. Active fractions were identified. Active compounds were next identified. The compounds from *Mammea Americana* include cobaltacene-octgomet, stigmastan-3,-diene, and friedelin.

Page 8, lines 8-16, emphasis added.

The Applicant explains the desire for the procedure that produces the more pure final fraction, expresses in two different manners that the methylene chloride extract is the superior extract in this respect (overall extracted material weight and complexity of the components of the initial extract), and re-states, outright, that the compounds in Table 5 are from methylene chloride:

> Example 3
>
> This example demonstrates that the anti-mycobacterial extract can be obtained by alternative extraction solvents and that a methylene chloride extract produces a more pure active fraction.
>
> • • •
>
> Tables 2, 3, and 4 present side-by-side the major ingredients in ethanol extracts and methylene chloride extracts of Mammea Americana. . . . The ethanol extraction was more effective in the retention of soluble material as indicated by the weight of the extracted material. In percentage of weight of starting material, the ethanol extraction yielded 18.7%, 1.6%, and 24.2%, while the methylene chloride yielded 1.46%, 0.26%, and 0. 73% of Mammea Americana, Merchantia polymorpha, and Callistemon citrinus, respectively.
>
> Furthermore, as can be observed from the side-by-side listing of the compounds identified by GC/MS in Tables 2-4**, there are fewer**

compounds in the methylene chloride extracts. Therefore, the active compound appears to be more pure when isolated by methylene chloride extraction.

. . .

[Example 4] **If the anti-mycobacterial compound (s) can be separated into a fraction containing yet fewer components, it may be possible to isolate a larger quantity of the active fraction which would be subject to renewed GC/MS analysis to identify the active compound of each plant of the invention.**

An HPLC separation and isolation of an active fraction was attempted. . . . As can be seen from Table 5, individual fractions having strong activities against E. coli and against M. smegmatis were identified. . . . **Based on consideration of the relative polarity and molecular weights of the compounds identified for the respective plants in the total methylene chloride extract, the compounds in the right-most column of table 5 "Additional Compounds" lists compounds which are not observed in the active fraction of the extract of the respective plants, but which are likely to be present in smaller quantities ("trace amounts") in the active fraction and which might contribute to the anti-mycobacterial activity.** (Emphasis added).

Clearly, the intent was to obtain a purer extract to facilitate purification, clearly the methylene chloride extract was the purer active extract, and, clearly stated, at least twice, the data presented in Table 5 is from processing the methylene chloride extract.

To arrive at the mistaken conclusion that the data in Table 5 is from material of the ethanol extract of the plant, the Examiner misreads the actual teachings of the specification. For example, the Examiner states that acetic acid was seen only in the ethanol original extract. But the specification expressly explains that only the major components could be detected in the initial cruder extract. The Examiner also notes that very point, when she notes that cobaltocene, stigmastan and friedelin were not seen in the HPLC analysis of neither original extract. So why is the lack of observation of acetic acid in the original extract such a crucial factor for the Examiner and the Examiner builds an argument around this fact? How is that different from, say, stigmastan showing up only in the analysis of the fraction? The Examiner may have misunderstood that point partially because the Examiner incorrectly notes that the other compounds on table 5 were identified in both extracts. By and large that is incorrect; however terpene was noted in both MA extracts.

The Examiner thinks phosphoric acid as an eluent off the column would not be appropriate for a methylene chloride extract applied to the column, OA, at page 9. The Examiner does not present support for this assertion. *See* page 22 in the specification for an explanation of what actually occurs. The elution is dictated by a combination of the MW and the polarity of the compound trapped on the column in relation to the polarity of the solvent for removal of the compound, without any connection of what was the solvent when the compound was first applied to the column.

It is abundantly clearly stated in the specification and reasonably understood that the Applicant presents in Table 5 data from GC/MSanalysis of fractions taken off a column loaded with material from extract of plant matter by methylene chloride.

The Examiner explains that there was motivation to identify and isolate the active ingredients, "as stated by Frame *et al*." The Applicant traverses. In respect to "isolation," in the past the Examiner has argued that in plant systems there is a good probability that an active composition may resist isolation. The Examiner has cited publications to that effect. That concern was shared by the Applicant. The specification states:

> If an extract with anti-mycobacterial activity by extraction with alternative organic solvents can be obtained, it would increase the likelihood that the active compound is a single compound or a very small number of compounds which could be isolated as a pure fraction. The alternative solvent tested was methylene chloride.

Page 18, lines 6-10. So, desire to identify compounds may be reasonably argued, but expectations of likely success are not presented in the cited prior art and absent in the artisan community at the time.

The Examiner acknowledges the lack of disclosure in the prior art of the presence of the compounds listed as elements of the claim, but dismisses the legal implication of that fact. However, the courts have repeatedly cautioned that obviousness can not be predicted on what is unknown. *See In Re Adams*, 363 F.2d 444, 150 USPQ 449 (CCPA 1966); s*ee* also 919 F.2d 688, 16 USPQ 2d 1897; 1922 (Fed. Cir. 1990) (en banc), certiorari denied 500 U.S. 904 (1991). The presence of these compounds in the M. Americana plant was not known.

The Applicant respectfully urges the withdrawal of the rejection under §103(a). The claims currently pending, both the newly presented and these previously presented, appear to be in condition of allowance.

If the Examiner believes there are any remaining issues, the Applicant's representative would very much appreciate a phone call from the Examiner, to expedite the prosecution by discussing these issues at the earliest convenience of the Examiner.

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By: /Michael David 44,642/
Dr. Michael David
Reg. No.: 44,642
Direct Tel. No.: (410) 347-9424

Whiteford, Taylor & Preston, LLP
Attn: Michael David
Seven Saint Paul Street
Baltimore, Maryland 21212-1636